

WHAT IS CLAIMED IS:

1. A method of removing a metal from a metal-containing liquid mixture, comprising contacting said liquid mixture with a solid extractant having a metal-binding functionality, said metal-binding functionality comprising an unsubstituted or substituted phosphine group, said metal-binding functionality being connected to said solid extractant directly or via a linking moiety which does not include at least one of a hydrocarbylsilyl residue or a polyamine residue.
- 15 2. The process of claim 1, wherein said metal comprises a soft acid.
3. The process of claim 1, wherein said metal comprises palladium.
- 20 4. The process of claim 1, wherein said metal-binding functionality comprises triphenyl phosphine.
5. The process of claim 1, wherein said solid extractant comprises a polymer resin.
- 25 6. The process of claim 1, wherein said solid extractant comprises a polystyrene resin and said metal-binding functionality comprises triphenyl phosphine.
- 30 7. The process of claim 1, wherein said liquid mixture comprises a liquid selected from the group

consisting of tetrahydrofuran, dioxane, acetone, water, acetic acid, methanol, ethanol, isopropyl alcohol, 1-butanol, 2-methoxyethanol, dichloromethane, chloroform, acetonitrile, benzene, toluene, xylenes, mesitylene, anisole, dimethyl formamide, hexamethylphosphoric triamide, dimethyl sulfoxide, N,N-dimethyl acetamide, diethyl ether, methyl t-butyl ether, diisopropyl ether, 1,2-dimethoxyethane, 1,2-dimethoxypropane, bis(2-methoxyethyl) ether, ethyl acetate, isopropyl acetate, ethyl propionate, ethyl vinyl ketone, butanone, hexanes, heptanes, octanes, cyclohexane, and mixtures thereof.

15 8. The process of claim 1, wherein said liquid mixture comprises a drug substance, or a precursor, intermediate, salt, solvate, or stereoisomer of a drug substance.

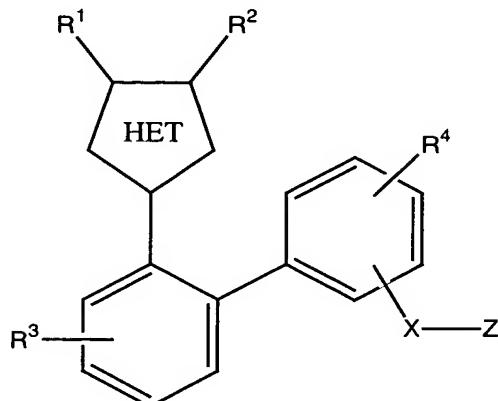
20 9. A method of recovering a drug substance from a liquid medium containing said drug substance together with at least one metal, said method comprising
25 contacting the liquid medium with a solid extractant having a metal-binding functionality, said metal-binding functionality comprising an unsubstituted or substituted phosphine group, said metal-binding functionality being connected to said solid extractant directly or via a linking moiety which does not include at least one of a hydrocarbylsilyl residue or a polyamine residue; and

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separating said drug substance from said liquid medium.

10. The method of claim 9, further comprising removing
5 said solid extractant from said liquid medium.

11. The method of claim 9, wherein said drug substance comprises a compound of formula I



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(I)

or a salt, solvate, stereoisomer, precursor, prodrug ester, or intermediate thereof, wherein

R¹ and R² are the same or different and are independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclo, and substituted or unsubstituted aralkyl;

R³ is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkylcarbonyl, polyhaloalkyl, cyano, nitro, hydroxy, substituted or unsubstituted amino, substituted

or unsubstituted alkanoyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkylaminocarbonyl, substituted or
5 unsubstituted alkylcarbonylamino, substituted or unsubstituted alkylcarbonyloxy, and substituted or unsubstituted alkylaminosulfonyl;

R⁴ is selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted
10 alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclo, substituted or unsubstituted aralkyl, substituted or unsubstituted arylalkenyl, substituted or
15 unsubstituted arylalkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, polyhaloalkyl, cyano, nitro, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkanoyl, substituted or
20 or unsubstituted aroyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or
25 unsubstituted alkylaminocarbonyl, substituted or unsubstituted arylaminocarbonyl, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkylaminosulfonyl, and substituted or
30 unsubstituted arylaminosulfonyl;

R¹, R², R³ and R⁴ may optionally be substituted with up to 5 substituents selected from the group consisting of hydrogen, halo, alkyl, polyhaloalkyl, alkoxy,

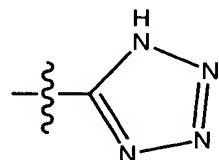
polyhaloalkoxy, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclo, aralkyl, arylalkenyl, arylalkynyl, aryloxy, arylazo, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heterocyclothio,

5 alkylcarbonyl, arylcarbonyl, acyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, arylsulfinyl,

10 arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, aminosulfinyl, aminosulfonyl, arylsulfonylamino, heterocyclocarbonylamino, heterocyclosulfinyl, heterocyclosulfonyl, alkylsulfinyl, sulfonamido and sulfonyl;

15 X represents a valence bond or a divalent linking moiety which can be read from left to right or vice versa and is selected from $(CH_2)_n$, $O(CH_2)_n$, $S(CH_2)_n$, cycloalkylene, $N(R^5)(CH_2)_n$, NHCO, or ethenyl, where n is an integer from 0 to 5, inclusive, and R^5 is hydrogen, alkyl, or alkanoyl;

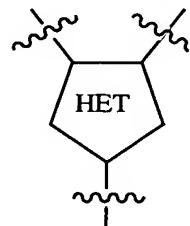
20 Z is COOR or a tetrazole of the formula



or its tautomer;

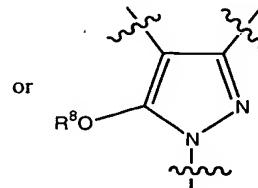
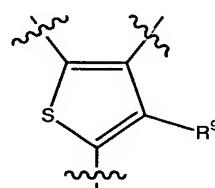
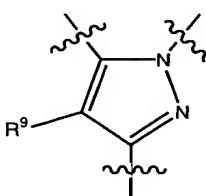
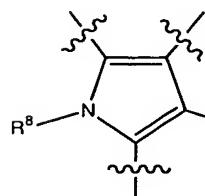
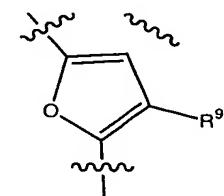
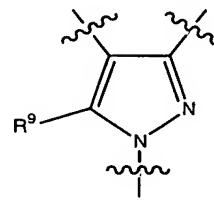
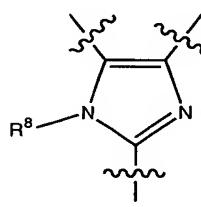
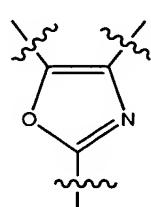
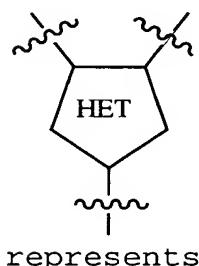
wherein R represents a radical selected from the group consisting of H, alkyl, aryl, aralkyl, cycloalkyl, heterocyclo, alkenyl, and alkynyl; and

25 the group



represents a heterocyclo group which may optionally be substituted with one or two substituents which are independently selected from the group consisting of alkyl, alkenyl, oxo, carboxyalkyl, carboxy, cycloalkyl, 5 alkoxy, formyl, alkanoyl, and alkoxycarbonyl, including all stereoisomers thereof.

12. The process of claim 11, wherein, in formula I,



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wherein

R^8 is hydrogen, alkyl, fluoroalkyl or alkoxyalkyl; and

R^9 is hydrogen, alkyl, fluoroalkyl, alkoxy or hydroxyalkyl;

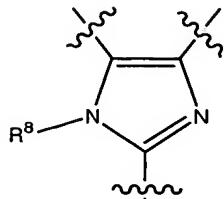
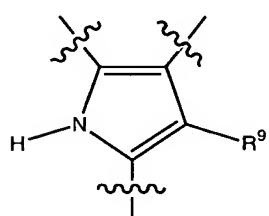
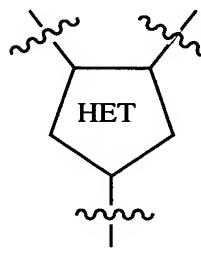
15 and wherein R^1 and R^2 are each phenyl, substituted phenyl or cycloalkyl;

R^3 and R^4 are the same or different and are independently selected from H, halo, alkyl or alkoxy;

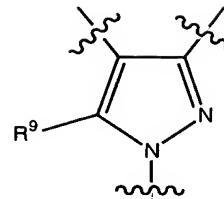
X is OCH₂, NHCH₂, CH₂ or CH₂CH₂; and
 Z is CO₂H or tetrazole.

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13. The process of claim 11, wherein, in formula I,



or



wherein R⁸ is hydrogen, alkyl or fluoroalkyl;

10 R⁹ is hydrogen, alkyl, fluoroalkyl or alkoxy; and

wherein R¹ and R² are each phenyl;

R³ and R⁴ are each hydrogen;

X is OCH₂, CH₂ or NHCH₂; and

Z is CO₂H or tetrazole.

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14. The process of claim 11, wherein said compound of formula I comprises 2'-(5-ethyl-3,4-diphenyl-1H-pyrazol-1-yl)-[1,1']-biphenyl-3-yloxyacetic acid.

20 15. The process of claim 11, wherein said metal comprises a soft acid.

16. The process of claim 11, wherein said metal comprises palladium.
17. The process of claim 11, wherein said solid extractant comprises a polymer resin.
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18. The process of claim 11, wherein said solid extractant comprises a polystyrene resin and said metal binding functionality comprises triphenyl phosphine.
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19. A method of recovering a drug substance comprising 2'-(5-ethyl-3,4-diphenyl-1H-pyrazol-1-yl)-[1,1']-biphenyl-3-yloxyacetic acid, or a salt, solvate, stereoisomer, precursor, prodrug ester, or intermediate thereof, from a liquid medium containing said drug substance together with at least one metal, said method comprising
15 contacting the liquid medium with a solid extractant having a metal-binding functionality, said metal-binding functionality comprising an unsubstituted or substituted phosphine group, said metal-binding functionality being connected to said solid extractant directly or via a linking moiety which does not include at least one of a hydrocarbylsilyl residue or a polyamine residue; and
20 separating said drug substance from said liquid medium.
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- 30 20. The method of claim 19, further comprising removing said solid extractant from said liquid medium.

21. The process of claim 19, wherein said metal comprises a soft acid.
22. The process of claim 19, wherein said metal
5 comprises palladium.
23. The process of claim 19, wherein said solid extractant comprises a polystyrene resin and said metal binding functionality comprises triphenyl
10 phosphine.
24. The process of claim 19, wherein said triphenyl phosphine comprises about 0.1 to about 10 mmol per gram of the solid extractant.
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25. The process of claim 19, wherein said PPh_3 comprises about 0.5 to about 3.5 mmol of the solid extractant.
26. The process of claim 19, wherein the solid
20 extractant is present at about 0.01 to about 10% of the weight of the liquid medium.
27. The process of claim 19, wherein the solid extractant is present at a weight of about 1 to
25 about 4% of the weight of the liquid medium.
28. The process of claim 19, wherein the liquid medium is contacted with the solid extractant at a temperature of about -20° to about 100°C .
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29. The process of claim 19, wherein the liquid medium is contacted with the solid extractant at a temperature of about 20° to about 60°C .